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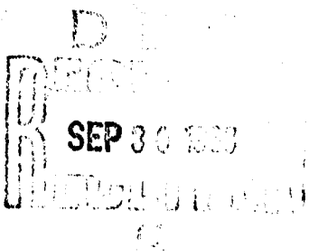

PARTICULAR ASPECTS OF THE ADRENAL CORTEX FUNCTION IN PULMONARY TUBERCULOSIS AND IN ASSOCIATED TB/DIABETES

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It is common knowledge that tuberculosis can take a multiplicity of forms, both in the symptoms that accompany its initial appearance, evolution, course and termination, and in the traces it leaves behind it in the host organism. It is no less variable in the range of causes that may determine it.

Attempts are made periodically to explain this property of TB on the basis of one or another of the factors even remotely related to it: etiology, bacterial strains and their variety in virulence, resistance, numbers, and point of entry into the organism, or again the host organism itself, human or animal, in which the disease develops, its constitution and its intimate structure.

Innumerable studies have been made of the mycobacteria, the immune responses, and the somatic, neural and endocrine constitution of TB victims. Certainly these bacteriological and related studies are essential. But no less important is the study of the affected organism.

For a number of years, a particular physical constitution known as the "phthysic look" was assigned great importance as a predisposing, if not a decisive factor in the transition from simple infection to serious illness, particularly in cases of pulmonary TB. Today this idea has lost much of its validity. We now lean, rather cautiously, towards the hypothesis that the physical constitution may, at the very most, allow certain

forms and phenomena of the disease to take hold. The individual makeup exerts its greatest influence in determining the seriousness of the disease and its course. (1) It is certain that advanced tuberculosis, in subjects who fall into the constitutional category known as "elongated asthenic" (with all the correlated diathesic weaknesses: exudative, thymolymphatic, etc.), does present a typical pattern in the majority of cases. These subjects are precisely the ones who are candidates for the chronic forms of apical tuberculosis (2).

Much, of course, has been said about the pre-disposing factors, most of them identified with those exogenous factors affecting the particular subject:nourishment, environmental conditions, hygiene, climate, and the like.

And yet, there are neurological and endocrinological factors, and hence factors relating to the individual's constitution and to his outside environment, which come into play in the onset of tuberculosis.

In clinical practise, however, the whole picture of symptoms associated with the manifestation of tuberculosis is very diversified, unfortunately, and, on the other hand, our ideas as to the precise nature of the pathogenic organism that causes the disease are incomplete. Hence the necessity for singling out, by means of studies of the specific functions of the organism, the constant and characteristic modifications that make it possible for the disease to gain a foothold, in whatever form it may assume.

Pulmonary tuberculosis, as a matter of fact, sometimes appears full-fledged, with the complete syndrome of the acute infectious form (high fever, toxic somnolence, tachycardia, hypotension). On other occasions, it comes on slowly, with all the symptoms attenuated (persistent low-grade fever, headache, anorexia, etc.). And, at still other times, its progress is completely masked, and the disease is far advanced when it is accidentally discovered.

Therefore, although we must agree that tuberculosis is a single etiological agent, the fact remains that there is not, in all its countless manifestations, a single symptom or diagnostic element to which we can point and say: "There: that is a basic phenomenon belonging to the clinical syndrome." We might call asthenia a common denominator: a careful scrutiny of available case histories would reveal its presence with a frequency closer to constant than any other single sign. But we should unquestionably run into problems were we to try to call asthenia the determining symptom. What might be done is to identify it

as a clinical manifestation of the cause of the disease, or consider it one of the effects of the unknown pathogen.

Currently popular is the theory that certain functional attitudes of the endocrine glands may so affect the organism as to predispose it to tuberculosis. The possibility that the pathogenic moment might be singled out as a particular abnormal state of some organic reaction has concentrated the attention of research workers on the operation of the pituitary and the adrenals. (3-4-5)

The influence of the pituitary on the insurgence and evolution of tuberculosis, despite all the study and attention devoted to it, is still far from being clearly understood. The findings of even the most recent studies in this area are wildly discordant with each other. There is not even universal agreement on the belief that the proneness to tuberculosis may be affected by removal of the pituitary. For example, Tonutti et al. (6-7-8) reported that one case of TB was aggravated by hypophysectomy, while Rössler (9) reported improvement following the same operation. Then, in addition, there is no lack of opinion (10) to the effect that removal of the pituitary has nothing whatever to do with either the onset or the development of the disease. In 1950, it was reported that sufferers from cachexia hypophysiopriva (11-12) were immune from tuberculosis. However, far from recent reports have it that during total or partial hypopituitarism there is less resistance to tuberculosis (13-14-15-16-17). These reports, furthermore, are based solely on clinical opinion, without any corroboration from laboratory data. Very careful studies by Grassi and his co-workers (18) failed to show any lessening in resistance to tubercular infection in rats after hypophysectomy. These Authors, however, have attributed special significance to these findings, for reasons which will be revealed subsequently. even though the Grassi findings may be superimposed on those of earlier experiments by Rössler (9) and Michael (19).

Again, the universally held opinion that ACTH and the adrenal cortex hormones were absolutely counter-indicated in tuberculosis has undergone complete revision. Just in the last few months, the findings of Lurie and his co-workers (20) on rabbits were confirmed by Spain's (21) work on guinea pigs, and lastly by Michael and his group (19) in their studies of rats. In those experiments it was found that animals which were normally resistant to tuberculosis became susceptible after treatment with cortisone. Bunn (23) reports that ACTH aggravates the tubercular infection in rabbits, and Selye (24) confirms this deleterious effect of the hormone in tubercular infections, and extends the indication to human pathology. Opposing interpretations of the effect came from Le Maistre (25), who maintains that the adverse

reaction should be attributed to pharmacological, rather than hormonal action, since the doses were excessive.

For that matter, even today, we tend to downgrade the findings of these pioneering experiments, particularly when we consider how readily ACTH can be made inactive. Most writers today agree that the reported aggravation of tubercular infection following administration of cortisone, administered in large doses, was mostly attributable to the antagonistic action of the hormone to simultaneous streptomycin therapy (26).

More recently, Grassi (27) reported that ACTH and cortisone aggravate the tubercular infection in rats, and at the same time make the animal more sensitive to exposure to infection. Applying his findings to human pathology, the same writer holds that treatment with ACTH or cortisone alone is counter-indicated in all forms of pulmonary tuberculosis. This writer does admit that such hormones may be used for more rapid resolution of the exudative processes, in association with specific antibacterial agents. He does limit this admission to the newer forms of the hormone, strictly ruling out any possibility of hormone therapy in the earlier forms. In conclusion, Grassi states that the adrenal cortex is the critical organ in the body's natural defenses against tubercular infection.

The lack of agreement on the effects of hypophysectomy derives, as we have already noted, from the observation that the adrenal cortex can continue its incretory activity for a considerable time after ablation of the pituitary.

Kass and his group (28) conducted a far more penetrating study on the comparative effects of corticosterone and hydrocortisone on resistance to infection. They conducted their research on rabbits, and used a method which allowed them to take blood samples from the adrenal veins. The data they gathered in this research led these writers to reason that: while hydrocortisone increases vulnerability to infection and adversely modifies the immune state of the organism, corticosterone, given in the same doses, plays no part in the production of antibodies. As a matter of fact, the antibody rate remains the same after all hormones are administered. Particularly interesting is the behavior of of ACTH in large doses, when it acts very like hydrocortisone in depressing the antibody production process. The writers, continuing their studies of the adrenal cortex function in the same animals, decided to approach the problem from the angle of the dynamic properties of the adrenals. They noted that prolonged stimulation with ACTH can induce a qualitative change in the secretion, involving changes in the ratios among the various steroid fractions. In these animals, after treatment with cortico-

tropin, the predominant steroid in the adrenal cortex secretion became hydrocortisone, instead of corticosterone as it had been originally. According to Kass, other stimuli of endogenous nature can affect the adrenal cortex, causing various and still undefinable changes in the quantitative output ratio of these two steroids.

Of extreme interest is the correlation between modification of the adrenal cortex secretions and resistance to tuberculosis. In this same study, Kass performed several experiments on rabbits genetically resistant to TB. The production of hydrocortisone was very high in both the sensitive and resistant strains, but the former secreted twice as much of it as did the latter. Stimulation with ACTH induces in some rabbits, irrespective of the fact that the total secretion is quantitatively less, a hydrocortisone output far higher than any found in genetically resistant animals which had been experimentally infected. All this, according to Kass's group, suggests that the tubercular infection causes a basic change in the functional attitude of the adrenals, and that this change affects not only the total quantity of steroid hormones secreted, but also, and far more, the quantitative balance among the various steroid fractions.

We find it eminently worth-while to lay special emphasis on the importance of this observation. For the first time, we see the accent put on the qualitative aspect of the adrenal cortex secretion, rather than on the purely quantitative one, and this is being done in connection with the physiopathology of the adrenal cortex in its relationship with tuberculosis. As we shall see later on, our own research will tend towards the same conclusions. After a series of inquiries, we were convinced that only through the study of the quantitative relationships among the various steroids, could we finally come to know the real functional purpose of the adrenal cortex, and the significance of its variations in the presence of tuberculosis.

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The study of the adrenal cortex function in man during the course of pulmonary tuberculosis, as covered in the literature, provides us with data concerning the behavior of the 17 urinary corticosteroids, which are all diminished in quantity (29-30), particularly in cases where the prognosis is grave(31)or in the chronic pattern (32).

Some writers claim to find a relationship between the concomitant liver damage and the dwindling excretion of the 17-KS.

In male subjects, they impute responsibility for the diminished urinary elimination of the 17-KS to the testicular hormones. (33-34-35).

Rarer, and in markedly less agreement, are references in the literature to the corticoids excreted in the urine. A diminution is reported (36), particularly in cases with accompanying neuro-vegetative disorders, and an increase (31) in cases where the prognosis is grave. There is no lack of writers who hold that excretion of these steroids is in no way influenced by the presence of tubercular infection.(30). We should like, however, to stress the fact that these data essentially reflect the marked disparity of of current opinion on the diagnostic value to be attributed to modern tests of adrenal cortex function, from the strictly technical point of view, and hence are of very slight value or utility in accurate orientation on functional symptomatology. While on the one hand it is well to keep in mind the monumental difficulty of obtaining uniform clinical evaluations on the aspects of a disease which provokes so many and such profoundly differing manifestations, we must also bear in mind the extreme complexity of the quantitative evaluation procedures required for the adrenal cortex steroids, which often mimic standards so different as to render any uniform interpretation of results difficult indeed. Add to this the fact that, very often, these same data are the expression of a "situational state" of the adrenal cortex, rather than a rounded picture derived from the exploratory dynamic study of the gland, including ACTH stimulation, which would provide us with a more reliable assessment of its functional state.

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The opportunity to attack the problem using time-tested methods and procedures (37-38) led us to conduct our investigations on subjects with pulmonary tuberculosis, of various types and in various stages of development of the disease, before and after stimulation with ACTH. We found it convenient to divide our cases into large groups, so as to gather, wherever it offered, a specific functional anomaly in different clinical patterns. We examined our cases individually, grouping them as follows: a) primary tuberculosis; b) post-primary: acute (phthysiogenous and non-phthysiogenous), chronic (cavitary and non-cavitary). Then in evaluating their behavior in urinary elimination of the corticosteroids, we shall follow this same order in Table 1.

Let us say right now that our case histories cover mostly female subjects. For one reason, most of the patients came from an exclusively female sanatorium. For the other, we deliberately chose female subjects in order to obviate the chance of urinary

excretions of testicular androgens, which might possibly distort the findings.

Primary tuberculosis --- Here, of course, because of the nature of the illness, we are dealing primarily with children, none of them over ten years of age, and in all of whom the appearance of the malady had been comparatively recent.

17-KS. Basal elimination, even in view of age and sex, was markedly low, with a considerable increase in the catabolytic components after administration of ACTH.

17-OH. Even though at very low limits, these can still be considered as falling within the bounds of the normal, with excellent response to ACTH stimulation.

CRT. The total reducing corticoids fall comfortably within the limits of the normal. However, we did discern a certain dissociation in the elimination of the corticoids themselves (change in the 17-OH/desoxy ratio).

Acute, non-phthysiogenic --- For all fractions, low basal elimination levels. Rsponse to ACTH, on the contrary, was invariably good. The desoxy fractions were well within the norm.

Acute, phthysiogenic --- 17-KS. Basal elimination in about 70% of these cases was low (grave cases), but some normal readings were found. Stimulation with ACTH, with the exception of the 4th, 17th and 19th cases, produced extremely scant response, sometimes so weak as to be almost undetectable.

17-OH. With the exception of case 17, there was a visible diminution in 60% of the cases. In the others, excretion levels were low, but still adequate to put them within the normal limits. The response to ACTH was consistently weak or absent.

CRT. With the exception of case 17, elimination was very scant, and response to ACTH weak or non-existent.

Chronic, non-cavitary --- 17-KS. Basal elimination values very low. Fair increase after administration of ACTH.

17-OH. Basal elimination values low or very low. ACTH response present, though not always marked.

CRT. Parallels the 17-OH fraction both in basal elimination and in ACTH response. Values for the desoxy fractions, however, were not far from the normal levels.

TABLE 1

URINARY ELIMINATION OF CORTICOSTEROIDS IN PULMONARY TB SUBJECTS BEFORE & AFTER

Nº	Id.	S	Age	Basal 17KS	Basal 17-OH	Basal CRT	Basal 17Desóx	After ACTH 17KS	After ACTH 17-OH	After ACTH CRT	After ACTH 17Desox	Diagnos
1	MG	F	12	1.21	1.2	2.8	1.6	5.9	1.4	2.0	0.6	Primary TB
2	DRA	F	13	3.72	2.16	3.30	1.24	6.08	3.86	4.30	0.34	Primary TB
3	MT	M	16	14.01	2.57	3.76	1.19	15.28	3.01	3.98	0.97	Primary TB
4	MC	F	28	1.9	0.98	1.6	0.7	3.2	1.8	2.1	0.3	Ac. non-ph
5	FR	F	17	2.1	1.8	2.2	0.4	4.2	2.4	3.0	0.6	Ac. non-ph
6	LA	F	45	5.1	3.6	4.8	1.2	9.4	3.8	5.6	0.8	Ac. non-ph
7	MG	F	27	10.10	2.0	2.07	0.7	15.5	2.7	3.3	0.6	Ac. non-ph
8	LL	F	36	4.6	1.7	2.3	0.6	6.2	2.5	3.0	0.6	Ac. non-ph
9	AD	F	42	4.2	1.9	2.7	0.8	8.6	2.3	3.0	0.7	Ac. non-ph
10	QR	F	44	3.9	2.4	3.4	1.0	6.0	4.1	5.0	0.9	Ac. non-ph
11	CC	M	31	16.5	1.4	2.1	0.7	26.0	2.2	2.0	0.7	Ac. non-ph
12	CR	F	20	7.13	2.86	3.16	0.7	8.26	2.78	3.10	0.18	Ac.phth.
13	SA	F	34	18.05	1.0	1.6	0.6	20.5	3.5	5.56	2.06	Ac.phth.
14.	DBB	F	21	24.8	1.0	1.6	0.6	13.6	1.6	2.1	0.7	Ac.phth.
15	DNM	F	23	3.4	2.1	3.2	1.1	4.2	4.2	4.4	0.2	Ac.phth.
16	PG	F	19	5.94	1.35	2.45	1.1	9.51	1.64	2.6	0.26	Ac.phth.
17	LO	F	16	6.38	6.87	7.9	1.03	9.52	8.54	9.32	0.78	Ac.phth.
18	CL	F	16	4.3	1.8	2.96	1.16	6.2	1.98	2.96	0.98	Ac.phth.
19	CN	F	20	4.0	1.01	1.3	0.29	8.1	1.4	1.9	0.5	Ac.phth.
20	GM	F	12	7.9	2.31	2.66	0.35	4.26	2.36	2.64	0.28	Ac.phth.
21	MF	F	13	5.9	1.6	1.9	0.3	6.1	2.1	2.8	0.7	Ac.phth.
22	SC	F	54	5.2	2.11	2.48	0.32	5.2	3.5	4.0	0.5	Ac.phth.
23	CR	F	30	3.6	1.4	3.6	2.2	5.4	2.9	3.8	0.9	Chr.non-cav
24	DDT	F	46	4.26	1.2	3.0	1.8	8.0	2.9	3.8	0.9	Chr.non-cav
25	DLR	F	30	3.2	1.6	2.0	0.4	7.2	2.7	3.9	1.2	Chr.non-cav
26.	CC	M	44	16.4	2.8	3.2	0.4	1.70	2.8	2.6	0.8	Chr.non-cav
27	LPV	M	43	10.2	2.2	3.3	1.1	14.4	Cr.Cr8	2.Cr6	0.98	Chr.non-cav
28	AZ	F	61	5.28	1.5	2.0	0.5	9.6	4.08	5.4	1.32	Chr.cavitar
29	DAP	F	56	9.0	2.28	3.5	1.22	10.0	3.86	4.2	0.34	Chr.cavitar
30	RC	F	20	12.0	3.4	3.8	0.4	11.4	4.2	4.8	0.6	Chr.cavitar
31	CS	F	34	7.54	3.12	4.0	0.88	9.2	3.0	3.6	0.6	Chr.cavitar
32	SS	F	22	4.6	2.1	2.9	0.9	5.4	2.6	2.8	0.2	Chr.cavitar
33	DMC	F	26	4.4	2.7	3.0	0.3	6.28	2.9	2.9	0	Chr.cavitar
34	SM	F	34	illegible	illegible	illegible	illegible	illegible	illegible	illegible	illegible	Chr.cavitar
35	MV	F	60	illegible	illegible	illegible	illegible	illegible	illegible	illegible	illegible	Chr.cavitar
36	CJ	F	30	illegible	illegible	illegible	illegible	illegible	illegible	illegible	illegible	Chr.cavitar
37	IG	F	16	illegible	illegible	illegible	illegible	illegible	illegible	illegible	illegible	Chr.cavitar

TABLE 1

PULMONARY TB SUBJECTS BEFORE & AFTER ACTH ADMINISTRATION (IN MG/24 HOURS)

After ACTH 17KS	17-OH	CRT	17Desox	Diagnosis	Remarks
5.9	1.4	2.0	0.6	Primary TB	Mos. Not grave.
6.08	3.86	4.30	0.34	Primary TB	Mos. Not gr.
15.28	3.01	3.98	0.97	Primary TB	
3.2	1.8	2.1	0.3	Ac. non-phth	Mos. Not gr.
4.2	2.4	3.0	0.6	Ac. non-phth	Many mos. Not gr.
9.4	3.8	5.6	0.8	Ac. non-phth	Many mos. Not gr.
15.5	2.7	3.3	0.6	Ac. non-phth	Many mos. Gr. Stationary.
6.2	2.5	3.0	0.6	Ac. non-phth	Many mos. Not gr. Improved.
8.6	2.3	3.0	0.7	Ac. non-phth	Many mos. Gr. Stationary.
6.0	4.1	5.0	0.9	Ac. non-phth	Many yrs. Not gr. Improved.
26.0	2.2	2.0	0.7	Ac. non-phth	Few yrs. Gr. Improved.
8.26	2.78	3.10	0.18	Ac.phth.	Recent. Not gr. Improved. Asthenia.
20.5	3.5	5.56	2.06	Ac.phth.	Sev.yrs. Stabilized. Grave. Asthenia.
13.6	1.6	2.1	0.7	Ac.phth.	Some yrs. Gr. Stabilized. Asthenia.
4.2	4.2	4.4	0.2	Ac.phth.	Sev.yrs. Gr. Fever. Asthenia.
9.51	1.64	2.6	0.26	Ac.phth.	Sev. yrs.Gr.Worsened. Asthenia.
9.52	8.54	9.32	0.78	Ac.phth.	Mos. Not gr. Cured.Asthenia.
6.2	1.98	2.96	0.98	Ac.phth.	Many mos. Not gr. Improved.
8.1	1.4	1.9	0.5	Ac.phth.	Mos. Not gr. Improved.No asthenia.
4.26	2.36	2.64	0.28	Ac.phth.	Mos. Not gr. Improved.
6.1	2.1	2.8	0.7	Ac.phth.	Mos. Not gr. Cured.
5.2	3.5	4.0	0.5	Ac.phth.	Few mos. Not grave.
5.4	2.9	3.8	0.9	Chr.non-cav.	Mos. Not gr. Improved. Asthenia.
8.0	2.9	3.8	0.9	Chr.non-cav.	Many mos. Not gr. Stationary.
7.2	2.7	3.9	1.2	Chr.non-cav.	Many mos. Not gr. Stationary.
1.70	2.8	3.6	0.8	Chr.non-cav.	Few yrs.Grave.Worsened.Asthenia.
14.4	0.08	2.06	0.98	Chr.non-cav.	Few trs.Grave.Worsened.Asthenia.
9.6	4.08	5.4	1.32	Chr.cavitary	Yrs.Not gr. Improved. Asthenia.
10.0	3.86	4.2	0.34	Chr.cavitary	Yrs. Mod.gr. Stationary. Asthenia.
11.4	4.2	4.8	0.6	Chr.cavitary	Yrs. Grave. Asthenia. Died.
9.2	3.0	3.6	0.6	Chr.cavitary	Yrs. Not grave. Asthenia. Stabilized.
5.4	2.6	2.8	0.2	Chr.cavitary	Years. Grave asthenia. Died.
6.28	2.9	2.9	0	Chr.cavitary	Yrs. Grave. Worsened. No asthenia.
7.3	3:6	4:7	1:1	Chr.cavitary	Yrs.Not gr. Stabilized. Min.asthenia.
12.0	2.2	3.6	1.4	Chr.cavitary	Yrs. Mod.gr. Improved. Min,asthenia.
10:1	1:8	2:8	1:0	Chr.cavitary	Yrs. Not gr. Improved. Min asthenia.
6.4	2.4	3.0	0.6	Chr.cavitary	Yrs. Grave. Asthenia. Worsened.

Chronic, cavitary --- 17-K. Low basal elimination values, with scant increase after administration of ACTH.

17-OH There is a lack of homogeneity in age here. Even in view of this consideration, we can confidently report that the basal elimination rate in more than 50% of the cases falls well within the limits of the normal, even though fairly low. Response to ACTH, however, is either scant or wholly lacking.

CRT. The basal values in about 75% of these cases falls inside the normal limits. This fact indicates a diminution of the desoxy portion, as compared with the preceding fraction, and a change in the 17-OH/desoxy ratio.

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At the outset, let's note the specific differences between the behavior of phthysiogenic and non-phthysiogenic forms of acute tuberculosis.

While the basal elimination is low in the non-phthysiogenic forms, and there is usually a response (though of widely varying degree) to ACTH, with the phthysiogenic forms there is usually a normal elimination rate, coupled with an ACTH response that is either very weak or totally lacking.

This peculiar behavior can be found again in a comparison between cavitary and non-cavitary forms. This leads to the notion that, in the phthysiogenic and chronic cavitary forms of TB, the adrenal cortex is working overtime, and at the very ceiling of its capacity. We are well aware that we are not telling anybody anything new here, especially in chronic cavitary cases. In these cases, we are dealing with a long and wasting illness, and the cortex is subjected to continual stimulation. That's why its failure to respond to ACTH is no surprise. It's just further proof that the gland is worn out.

We find the study of the reported levels of the desoxy group of corticosteroids much more interesting. Here we can glimpse a dissociation in the urinary elimination of the corticosteroids, an alteration in the balance between the 17-OH and desoxy groups, which is occasionally more marked after ACTH stimulation. This is particularly evident in some of the chronic non-cavitary cases, a group which, in our experience, showed less marked asthenia, on the whole, than the usual group of TB patients.

In pursuing our study of the incretion of the adrenal cortex, we made an evaluation, along with that of urinary excretion,

Table 2 - Quantitative anlysis of plasmatic steroids in pulmonary TB patients. (In mg per 100 ml plasma.)
ACTH administered by slow intravenous infusion.

	Number	Initials	1st elution	17-OH	CRT	17-Desoxy
BASAL	7	M.G.	120	22	34	12
	8	L.L.	160	29	43	14
	9	A.D.	150	21	29	8
	13	S.A.	180	26	44	18
	14	DB.D.	190	36	56	20
	19	C.N.	220	40	62	22
	23	C.R.	110	20	36	16
	27	L.P.V.	165	38	49	11
	28	A.Z.	140	22	42	20
	34	S.M.	135	24	48	24
3 HRS POST-ACTH	7	M.G.	160	26	36	10
	8	L.L.	180	32	44	12
	9	A.D.	160	27	33	6
	13	S.A.	170	29	40	11
	14	DB.D.	200	48	60	12
	19	C.N.	240	50	60	10
	23	C.R.	145	58	32	14
	27	L.P.V.	180	51	60	9
	28	A.Z.	180	24	44	20
	34	S.M.	170	28	44	16
6 HRS POST-ACTH	7	M.G.	130	26	34	8
	8	L.L.	150	30	40	10
	9	A.D.	130	23	28	5
	13	S.A.	180	28	40	12
	14	Db.D.	175	44	58	14
	19	C.N.	220	40	52	12
	23	C.R.	120	20	32	12
	27	L.P.V.	170	36	46	10
	28	A.Z.	150	24	40	16
	34	S.M.	140	22	36	14

in ten subjects previously studied by us, of the quantitative aspect of the plasmatic steroids, using a method we developed ourselves (39), before, during, and after venous administrati n of ACTH. Our results are summed up in Table 2. As you can see, the basal values for all fractions are consistently low. Even lower levels were encountered in particularly grave cases.

The response to ACTH brings out an evident dynamic insufficiency, which is markedly more acute in the grave cases.

We also observed a quicker turnover of the steroids and a particularly high level of corticosterone derivatives, which diminished after ACTH stimulation in patients with cavitary TB.

On the basis of these findings, we decided it might be fruitful to carry the inquiry further, and to evaluate, in some of the subjects we had previously observed, the amounts of the individual steroid fractions of adrenal cortex origin eliminated in the urine.

For this purpose, using a technique we worked out for ourselves (38-39), we charted what we call the "chromatographic profile."

The extreme complication of the inquiry forced us to limit the number of cases. However, we should like to emphasize here that our primary concern was to evaluate the quantitative relationships among the individual adrenal cortex steroids. We expressed this ratio in percentage form (Table 7), and we also evaluated the ratios of the main adrenal cortex steroids (E, F, DOC, B) along with the respective tetrahydro-derivatives.

Then in Table 3, we show the results we found in measuring amounts of the individual steroid fractions as separated by paper chromatography, using the urine of 8 TB patients in various stages of the disease.

We worked out an average, or mean, chromatographic profile for urinary elimination of the corticosteroids in TB patients, and compared it with an equivalent profile for normal subjects (fig. 1). We did not extend this inquiry into the individual clinical varieties for the same reasons that compelled us to limit the number of our experimental cases.

In our group, as compared with normal subjects, we found a high level of E and F compounds, including their respective H_4 derivatives. Involved here, too, are the levels of the B-group compounds (allox- and tetrahydro-derivatives), with a

Nº	Init.	H_4F	H_4E	F	E	H_2E	H_4B	Allo H_4B	B	H_4S	H_4 DOC	DOC	Uni-dent	Total	K	17-OH	Aldo-sterone
8	MT	180	480	125	65	26	108	120	160	---	10	8	48	1330	0.9	1470	2.8
13	SA	310	1110	169	98	38	180	210	270	16	8	10	36	2549	0.85	2870	2.6
15	DN.M.	270	730	135	80	30	150	164	200	10	10	8	42	1827	0.87	2100	4.6
16	PG	150	480	120	60	20	100	110	133	--	--	6	26	1215	0.90	1350	8.2
23	CR	120	510	100	65	22	90	125	170	--	10	12	64	1288	0.92	1400	5.8
28	AZ	170	550	130	80	24	105	125	140	--	12	4	40	1380	0.92	1500	18.5
29	DA.P.	244	654	110	80	30	160	210	260	14	12	10	38	1842	0.88	2280	7.6
33	DM.C.	320	840	162	100	40	210	290	246	12	14	16	72	2322	0.86	2700	1.4
Mean:		222	670	131	78	29	114	172	198	13	11	9	--	1766			
Reference norm.aver.		600	1900	320	185	80	420	525	480	25	20	30	19	4604			

TABLE 3. - Analysis of the quantities of individual steroid fractions identified in the urine of pulmonary TB patients. Values, expressed in mg, are the totals excreted in 24 hours. (Note: Case-numbers used refer to Table 1, which shows urinary elimination of corticosteroids in the same subjects.)

relative diminution of about 24% of the total amount. The B compound as such, however, would seem to show a general increase, if the sum total of the subjects were considered. This gain is not, however, to be found in each individual case. As a result, the ratio between the B compound and the respective H_4 derivatives also increases (Table 7). For DOC, we found a marked drop, with a relative increase in the corresponding tetrahydroderivative, and a resultant lowering of the ratio. It is noteworthy that wherever the drop in DOC is most marked, there is a relative rise in B. In this case, we also noted a sharp increase in the aldosterone content of the urine. It seemed to us that there was an inversely proportional ratio, albeit not very clearly defined, between DOC and aldosterone. For several of our subjects, we made paper chromatographs after stimulation with ACTH. Although we do not show this data graphically, we can report that the corticotropic stimulus, even though it did not produce any real increase in total secretion of corticoid hormones, does tend to bring the chromatographic profile back towards the normal pattern, to the point where there is a normal percentage relationship established among the several fractions.

In conclusion, it is our impression that there exists in tuberculosis patients, as compared with normal subjects, a heightened E, F, B /H_4 derivates ratio, because of the relative drop in the corresponding catabolic hydroderivatives; and that there is, on the contrary, a lowered DOC/H_4DOC ratio, owing to the drop in DOC and the simultaneous rise in H_4DOC.

From what we have stated thus far, it seems that we can safely state that while the TB victim does not display the usual symptoms of the "static" hypoadrenal patient, except in cases of exceptional severity, he invariably reveals some degree of dynamic adrenal insufficiency.

This is quite independent of the qualitative variations in the secretions we were able to uncover. We felt it extremely challenging to complete our study of the adrenal cortex, extending it to specially selected tubercular patients, in whom the adrenal cortex is necessarily involved in the physiopathy of the syndrome: TB patients with coincident diabetes.

We had already conducted several inquiries into the function of the adrenal cortex, using the same procedure, on diabetic subjects, and we refer the reader to our earlier reports on this aspect (42, 43- 44, 45). Here, we should simply like to point out the interesting part of the inquiry from this point of view lies in the discovery of the almost invariable absence of hypoadrenalism, either static or dynamic, in the diabetic syndrome. This would seem to indicate that the presence of

TABLE 4. - Corticosteroid elimination before and after ACTH in subjects with associated pulmonary TB and diabetes. Quantities given in mg/24 hours. N.B. All subjects in metabolic equilibrium: glycemia 1.70g‰ max., no glycosuria, no ketonuria, normal alkaline reserve (50-60 ml CO_2% of plasma).

Nº	NS	Age	Diagnosis	Glycemia		Base	Post ACTH	ACTH Resp.	Remarks
1	CP	m 47	Incipient TB	1.45	17-KS	13.20	16.30	0	Grave diabetes, mild TB. Improved.
					17-OH	3.97	4.08		
					CRT	4.90	5.00		
					17-desossi	0.93	0.92		
2	MN	f 52	Ac.non-phth.	1.30	17-KS	6.36	8.50	+++	Recent diabetes. TB not grave.
					17-OH	3.90	3.28		
					CRT	4.83	6.00		
					17-desossi	0.93	0.32		
3	DB	f 60	Acute, phth.	1.70	17-KS	3.44	5.20	++	Grave diabetes. TB not gr. Improved.
					17-OH	2.37	4.52		
					CRT	3.73	4.60		
					17-desossi	0.63	0.80		
4	MF	f 31	Acute, phth.	1.60	17-KS	3.02	4.32	+±	Both diabetes and TB grave. Died.
					17-OH	1.50	2.28		
					CRT	1.93	2.28		
					17-desossi	0.43	0		
5	DD	f 60	Chron. non-cav.	1.40	17-KS	12.10	15.00	+	Mild diabetes. Mild TB.
					17-OH	2.80	3.94		
					CRT	3.20	4.10		
					17-desossi	0.40	0.70		
6	MG	f 60	Chron. non-cav.	1.60	17-KS	6.42	9.30	+	Grave diabetes, mild TB. Improved.
					17-OH	3.40	4.20		
					CRT	4.80	5.28		
					17-desossi	1.40	1.08		
7	SP	f 60	Chron. non-cav.	1.40	17-KS	12.00	12.40	0	Grave diabetes and TB. Improved.
					17-OH	5.64	5.80		
					CRT	6.54	6.70		
					17-desossi	0.90	0.90		
8	CI	m 46	Chron. non-cav.	1.35	17-KS	12.60	16.80	±	Mild diabetes, grave TB. Improved.
					17-OH	4.78	5.40		
					CRT	5.40	5.90		
					17-desossi	0.62	0.30		
9	SC	f 56	Chron. cavitary	1.60	17-KS	5.80	7.23	0	Grave diabetes and TB. Died.
					17-OH	3.01	3.12		
					CRT	3.46	3.12		
					17-desossi	0.45	0		
10	SA	f 22	Chron. cavitary	1.40	17-KS	9.20	14.80	0	Grave diabetes and TB. Improved.
					17-OH	3.00	3.94		
					CRT	4.08	4.73		
					17-desossi	1.38	0.79		
11	DA	f 61	Chron. cavitary	1.70	17-KS	8.80	10.00	0	Grave diabetes, very grave TB. Died.
					17-OH	2.80	3.90		
					CRT	3.00	3.60		
					17-desossi	0.20	0.70		
12	DMG	f 40	Chron.cavitary	1.50	17-KS	7.48	12.80	0	Grave diabetes, very grave TB. Died.
					17-OH	3.40	3.06		
					CRT	4.86	4.28		
					17-desossi	1.46	0.32		
13	MB	f 62	Chron. cavitary	1.30	17-KS	4.28	5.70	++	Mild diabetes and TB. Stabilized.
					17-OH	3.02	4.40		
					CRT	3.80	5.00		
					17-desossi	0.78	0.00		
14	LP	m 50	Chron. cavitary	1.60	17-KS	7.00	14.20	0	Mild diabetes, grave TB. Improved.
					17-OH	3.04	3.30		
					CRT	6.12	6.00		
					17-desossi	1.08	0.70		
15	CT	m 48	Chron. cavitary	1.50	17-KS	10.20	11.40	±	Mild diabetes and TB
					17-OH	4.02	4.84		
					CRT	4.92	5.88		
					17-desossi	0.90	0.44		

diabetes would, ipso facto, preclude any adrenal insufficiency, or, in any case, that the functional state of the adrenal cortex is the determining factor in the appearance and persistence of the disease. This leaves a wide-open field for discussion as to whether the dysmetabolic syndrome can or cannot appear in the course of tuberculosis; whether or not, if it does coexist, it must necessarily have pre-dated the onset of the TB infection, at least in the latent state, with all the factors commonly held to predispose towards or favor the appearance of diabetes: family history, endocrine constitution, dietary habits, and so on. As to the appearance of diabetes in tubercular patients, there has already been considerable discussion. Tuberculosis is a long-term, wasting disease. It is primarily a toxic one, and that very toxicity, over a long period of time, might very well be singled out as the prime factor in the causation of pancreatic lesions. At the same time, the metabolic disorders consequent upon it exert a harmful effect on a chronic disease such as tuberculosis. And, as a matter of fact, it is a common clinical observation in cases where the two diseases are coexistent that the diabetic condition improves as the tubercular infection heals.

Statistics on the two diseases in association are not altogether in agreement. This is because of the reflected effect of the fact that, while TB attacks primarily young people (and even though the percentage of TB infection in infancy and childhood has recently been sharply lowered, in some 50% of all cases, TB still appears during the first 25 years of life), diabetes generally strikes after 25 (46).

The frequency of association between tuberculosis and diabetes reported by Joslin (52) in a report published at a diagnostic center in the United States, covering the period from 1898 to 1951, shows 836 cases of associated diabetes in 32,148 tubercular patients, for a total of 2.6%. Earlier statistics (1944) from Neogy and Roy (53) give higher association percentages: 3.3%, but on a smaller number of cases (1882).

We should also remember that an inquiry by Boucot (54) and his group, on 3,000 diabetics, showed that the incidence of tuberculosis among the diabetic population was double that among non-diabetics.

Considerably lower association statistics are reported on patients cared for in sanatoria (52), among whom the incidence of associated diabetes is about 0.5%.

We have ourselves the data on some 2,000 sanatorium patients, among whom the cases of associated TB and diabetes come

to 20, or an incidence of about 1%. This is about the same level as was reported by the INPS TB outpatient service, covering about 6,000 cases treated during the 1950-1960 decade.

Still in the statistical field, we find several writers who maintain that women are less prone to the association of the two diseases than are men (45).

As for the appearance of diabetes during the course of tuberculosis, the statistics are not in agreement, although all cite very small percentages. Montgomery's cases (47), reported by Massari and his group (49) showed percentages of about 0.16%.

Root (47) admits that in 20% of all cases, tuberculosis can antedate diabetes; but we find, with Ritz (48) that no such eventuality can be reliably established.

Our experience has taught us how very difficult it is to keep a precise record of every patient. The data we gathered on a diabetic population in which discovery of a coexisting form of pulmonary infection was quite accidental (out-patients, clients at a diabetes diagnostic center, and the like) are as shaky as any statistics can be insofar as the date of insurgence of the TB infection is concerned. All we had to go on were vague, subjective data: low-grade fever, exhaustion, sweats, and the like.

At the same time, those cases in which we can document the time of insurgence of diabetes during the course of tuberculosis are almost all hospitalized patients in sanatoria, in which discovery of latent diabetes is not always possible, since standard procedure does not call for a thorough metabolic check on every hospitalized subject.

It is our final impression that, while in a very great number of cases it is unquestionably correct to diagnose diabetes as antedating tuberculosis, in no case is it possible to establish irrefutably the pre-existence of TB.

We would note here that, quite apart of the order of appearance of the two diseases, their association produces a clinical state of tuberculosis which can generally be reduced to the exudative-caseous stage (51) (charged to the fat metabolism dysfunction of the diabetic)(56), or to generally parailiary infiltrative lesions, interpreted as "healing allergy adenopathy" (56), or, lastly, to forms marked by heavy coinvolvement of aspecific bacteria in the tubercular foci (50).

Tuberculosis is often diagnosed late in diabetics.

The marked loss of weight, the unexplained worsening of the established TB syndrome may well arouse suspicions of associated diabetes (52), just as, on the contrary, a diabetic whose condition worsens without any apparent cause should alert his physician to the possibility of tuberculosis. It is common knowledge that aggravation of the tubercular picture, or indeed any form of serious TB, exerts a most unfavorable influence on diabetes, making its treatment particularly difficult.

In cases of advanced tuberculosis, the diabetic may get beyond control by standard therapy. Coincident with the appearance of sugar in his urine, he develops a dangerous sensitivity to insulin. In a hyperglycemic coma, he may prove insulin-fast, as happened in the case cited by Grafe (56), in which a TB patient in diabetic coma required 2770 U of insulin.

Blood-sugar variations in tubercular diabetics are similar to those in other diabetics, unless there are coexisting adrenal or hepatic lesions.

Although the onset of tuberculosis in the diabetic is often insidious, it is by no means rare to encounter forms of the disease whose onset is lightning-swift, or at least very fast. In general, however, the prognosis is no different from that of uncomplicated cases.

Whatever the mechanism or the order of insurgence of the two diseases in the morbose association, we believe that consideration should be given to the functional state of the adrenal cortex as one of the factors of crucial importance.

This is why the problem of possible insurgence of a diabetic syndrome in hypoadrenal patients should be considered of the first order of interest. Examination of selected cases exhibiting this particular profile, as we have several times pointed out, allows of useful clinical deductions, including some in the area of adrenal cortex pathology.

This is why we investigated the function of the adrenal cortex, using the very same procedures outlined above for tuberculosis patients, on 15 subjects suffering from associated TB and diabetes.

In every case, the diabetes antedated the tuberculosis. At the time of our examination, none of the subjects showed a blood-sugar level higher than g.1.70/oo. Glycosuria and ketonuria were absent, R.A. normal.

In our initial series of experiments, we analyzed urinary elimination of steroid hormones before and after stimulation with ACTH. Our results are shown on Table 4.

The elimination of steroid hormones of cortical origin in our patients showed no basic difference of pattern from that of uncomplicated diabetics (41), varying from the normal only in a consistently higher level of excretion.

ACTH stimulation, however, reveals a dynamic adrenal cortex insufficiency. We noted, at the time, a parallel between such insufficiency and the gravity of the tuberculosis.

The proportion of desoxycorticoids is very high, compared with normal subjects as well as with non-diabetic TB patients. Unlike the situation in other morbose conditions involving high excretion of 17-desoxy fractions (hepatic affections, uncomplicated diabetes, etc.), this one does not always respond to ACTH stimulation with a lowering of secretion levels.

The basal elimination of steroids in the urine in tubercular diabetics apparently follows the pattern of diabetes, rather than that of tuberculosis. The values we found for excretion were largely within the normal limits, whereas non-diabetic TB patients generally show low excretion levels, particularly those with non-phthysiogenic or non-cavitary forms of the disease.

We also analyzed the plasmatic steroids in ten of our subjects, before, during and after intravenous administration of ACTH.

As you can see from the results shown in Table 5, there is a parallel with the findings of our study on urinary elimination of the corticosteroids.

The basal values differ from those of normal subjects as well as from those of non-complicated tubercular subjects in being generally higher.

Response to ACTH stimulation, however, was pretty much the same in patients with associated TB and diabetes and those with simple TB. Both are lower than normal, even though they show a faster turnover. The response here, however, is less marked than in non-tubercular diabetics.

To complete this portion of our inquiry, we did paper chromatographies on 8 of our subjects. As Table 6 shows, these were mainly chronic cavitary patients. We selected these people

Table 5. - Quantitative analysis of plasmatic steroids in subjects affected with both pulmonary TB and diabetes mellitus. Values are given in µg per 100 ml of plasma. [illegible] was performed by slow intravenous infusion. (NOTE: Case numbers refer to Table 4, showing urinary elimination.)

N.	Inis.	BASAL				4 HRS AFTER ACTH				6 HRS AFTER ACTH			
		1ª eluzione	17-OH	CRT	17-deson.	1ª eluzione	17-OH	CRT	17-deson.	1ª eluzione	17-OH	CRT	17-deson.
1	C. P.	120	58	76	18	140	68	83	15	161	64	78	11
2	M. N.	150	48	58	10	160	50	59	9	180	58	66	8
4	M. F.	190	44	62	18	195	42	52	10	210	46	58	12
5	D. D.	195	52	62	20	210	58	70	12	255	58	70	12
8	C. I.	215	46	60	14	230	48	57	9	230	40	50	10
9	S. C.	210	38	54	16	210	40	49	9	220	46	56	10
10	S. A.	150	60	75	15	160	65	79	14	190	70	84	14
11	DA. F.	170	40	54	14	180	42	53	11	190	42	52	10
12	DM. G.	175	34	68	34	180	36	47	11	205	40	60	20
13	M. B.	100	26	52	26	120	28	42	14	140	28	50	11

Table 6. - Quantitative analysis of the individual steroid fractions identified in the urine of subjects affected with both pulmonary TB and diabetes mellitus. Values given in µg referred to the total excreted in 24 hours. (NOTE: Case numbers refer to Table 4, showing urinary elimination of corticosteroids in the same subjects.)

N	Inis.	H_4F	H_4E	F	E	H_4E	H_4O	Allo H_4B	B	H_4S	A	H_4 DOC	DOC	Non ident.	Totale	K	17-OH	A [illegible]
1	C. P.	473	1103	303	265	110	273	290	265	19	12	16	10	26	3570	0,90	30,0	4 [illegible]
2	M. N.	435	1343	375	245	95	270	270	225	18	12	18	18	23	3350	0,80	30,0	[illegible]
3	D. B.	296	964	270	175	75	185	207	162	13	9	18	14	47	2110	0,85	25,0	1 [illegible]
5	D. D.	316	950	270	190	75	196	215	170	13	8	13	13	16	2160	0,88	28,0	[illegible]
10	S. A.	372	1150	288	230	98	232	260	210	20	11	19	16	18	3020	0,84	30,0	8 [illegible]
12	D.M.G.	395	1175	350	244	85	240	290	230	17	11	15	16	21	3060	0,90	31,0	[illegible]
14	L. P.	586	1770	386	305	105	305	395	320	25	17	23	24	33	4030	0,92	30,0	[illegible]
15	C. T.	470	1360	400	261	120	272	305	251	19	12	18	19	26	3515	0,88	40,0	5 1
1	Media	418	1303	373	247	103	254	273	231	18	12	17	17	30	3534			
2	Media normali	660	1900	320	185	80	120	325	480	25	—	20	30	19	4604			
3	Media diabetici	616	1709	332	402	116	323	414	329	21	15	24	30	31	4451			
4	Media tbc.	232	670	131	78	39	114	172	106	13	—	11	9	—	1766			

1 = [illegible]
2 = Normal mean
3 = Mean for diabetics
4 = Mean for TB subjects

Fig. 1. - Mean results of 8 chromatographic analyses of the urinary steroids in pulmonary TB subjects. Above are shown the respective UV-Rf's with their absorption spectra in ultraviolet, by means of which we identified the steroids. Values are shown for an average daily diuresis of 1500 ml and for λ = 0.69. Shaded portions indicate normal mean profiles.

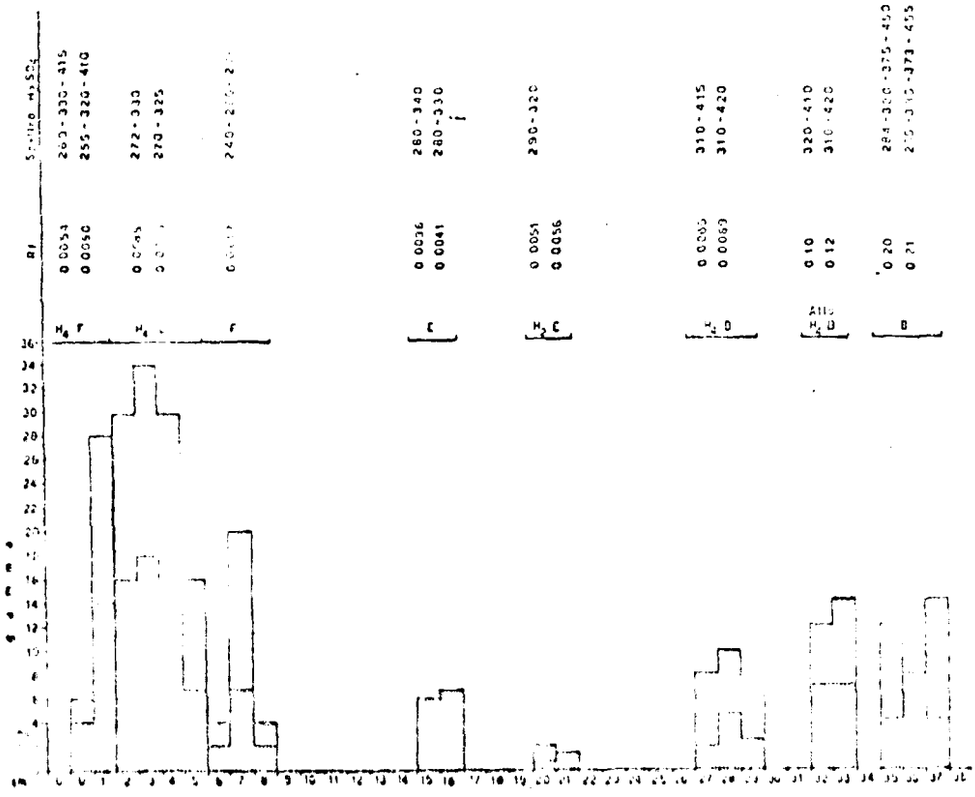
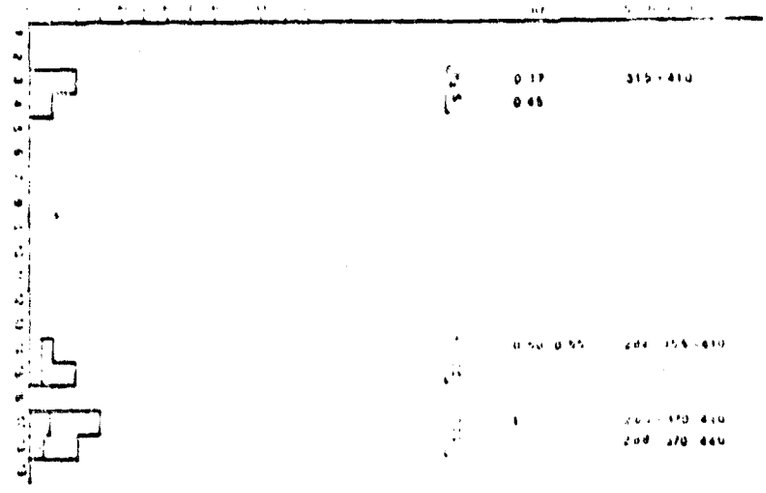


Figure 1

Figure 1
(continued)



largely because this was the most prevalent [illegible] among [illegible] jects available (more than [illegible]).

With these subjects, all of whom, as we have noted, were in perfect metabolic balance at the time of the tests, we evaluated the single steroid fractions eliminated in the urine, including aldosterone, using the same techniques [illegible] for our tubercular subjects, using [illegible] chromatography.

On the graph (Fig. 2) we show the profile [illegible] with a normal chromatogram in order to make the variations more visible. In figure 3, we have diagrammed the chromatographic profiles for the various morbose situations hitherto discussed, and compared them with the normal.

As you can see, both the diabetic [illegible] and the tubercular diabetics differ from the norm to a [illegible] degree, insofar as the F and F compounds and their reduced [illegible] derivatives are concerned. Both the F/Hg F and the F/Hg F values show an increase, owing to the relative increase of the F and F content (Table 7).

The increase in the tubercular diabetics, however, can also be attributed to a drop in the Hg derivatives, while [illegible] happens in the case of simple diabetes.

As for group B and its Hg derivatives, we find a [illegible] contrast between the picture for the non-diabetic TB patients and the low relative B fraction for diabetic TB subjects. Here we see a drop in the B/HgB ratio, though not so marked as the one for non-tubercular diabetics.

The visible drop in the [illegible] ratio following a rise in the [illegible] fraction can be charged to the constant and more evident increase in the Hg[illegible] fraction. From this aspect, the chromatographic profiles of the diabetic and non-diabetic TB patients show more similarity, and both are sharply distinguished from that of the non-tubercular diabetic.

Finally, as for aldosterone in the urine, we found low readings, some of them at the lower limits of the normal, except for two cases which were altogether normal.

Discussion and conclusions

From what we have thus far stated in connection with the functional condition of the adrenal cortex in tuberculosis patients, we feel that we can draw several sound conclusions.

. 2. – [illegible] analyses of the uri-
[illegible] to the
[illegible] in sedimentary
[illegible]. Values are
[illegible] for K = 0.88.
[illegible] thermal neutron profiles.

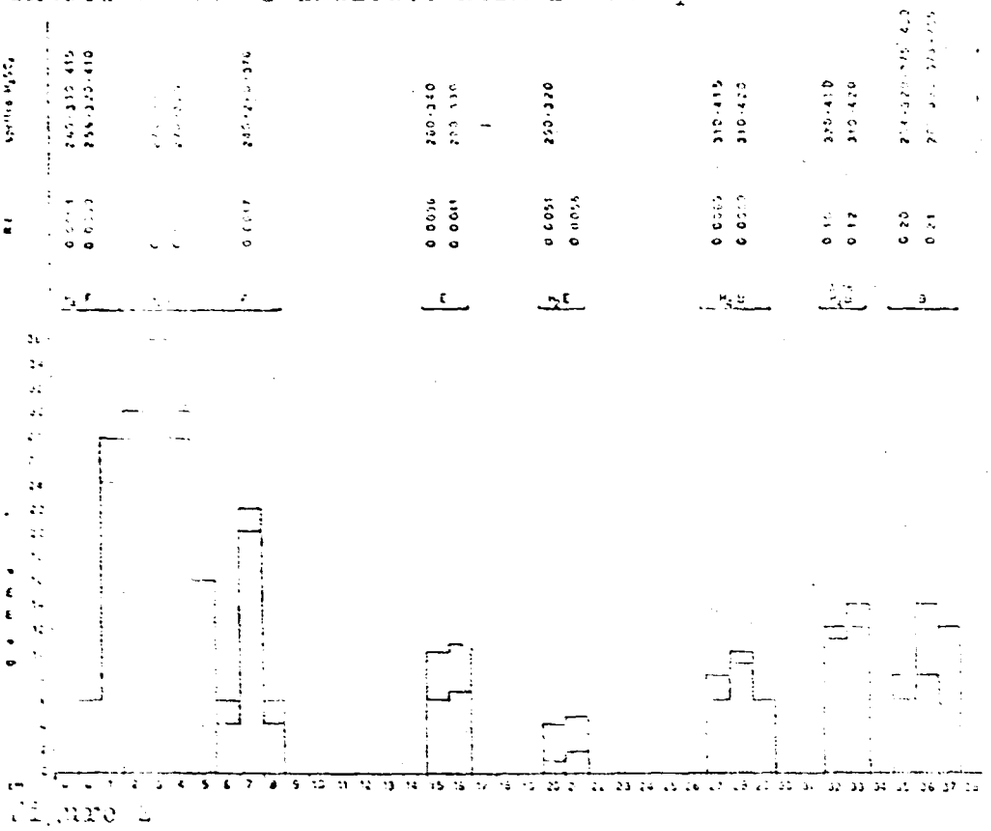
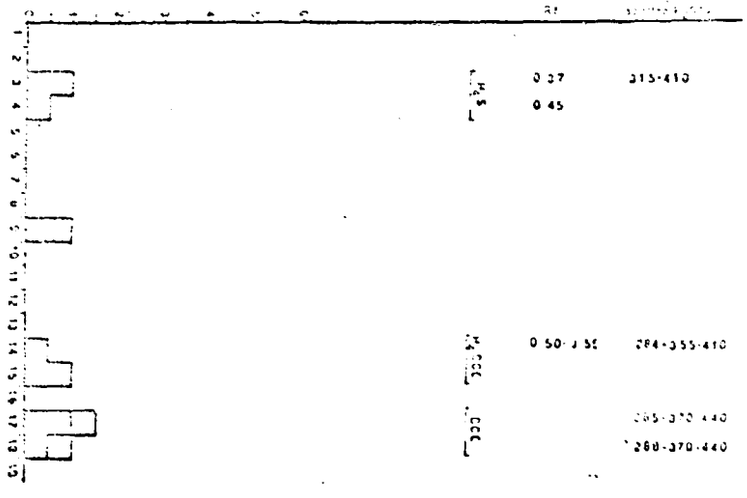


Figure 2
(continued)



The tubercular individual does not necessarily reveal a static adrenal cortex insufficiency. Actually, his basal elimination of urinary steroids of cortical origin often falls within the limits of the normal , as may his basal plasma levels of corticosteroids.

It is easier, though, to detect dynamic insufficiency after corticotropic stimulation. This insufficiency is encountered with greater frequency in some clinical varieties of tuberculosis. While it is not possible to correlate the functional state of the adrenal cortex with the gravity of the TB affection, there is a clear relationship between it and the phthysiogenous evolution.

On the other hand, we were unable to find any relationship whatever between the condition, either static or dynamic, of the adrenal cortex and a number of clinical symptoms of tuberculosis, particularly, as we reported, between cortical condition and asthenia.

In this connection, we should like to refer again to case 17 in our study. Here we found a particularly high proportion of hydroxy-steroids eliminated in the urine, coupled with a very marked asthenic syndrome.

Since similar observations can be made in connection with the study of the hematic steroids, we feel justified in attributing no determining significance to quantitative variations in adrenal cortex function, at least insofar as the possibilities of finding a correlation between these fluctuations and any clinical symptom, such as asthenia, are concerned.

We do feel, though, that while considerable difficulty is involved in making an exact evaluation of the functional capacity of the adrenal cortex, it is just as difficult to interpret its variations. The problem here is to decide whether these variations should be taken as determining, or at least favoring the onset and evolution of the morbose syndrome, or whether they are simply its inevitable consequences.

It is our belief that each clinical case has its own specific character, and that much of the findings on adrenal cortex function should be integrated into the general adaptation syndrome. Hence it is only on rare occasions that we can find, to within any acceptable degree of accuracy, the particular dynamic orientation that might have allowed, if not caused, the onset and establishment of the disease.

Deductions of a physiopathological order, on the other hand,

Fig. 3 - Graph of chromatographic profiles in the various morbose situations as compared with the normal.

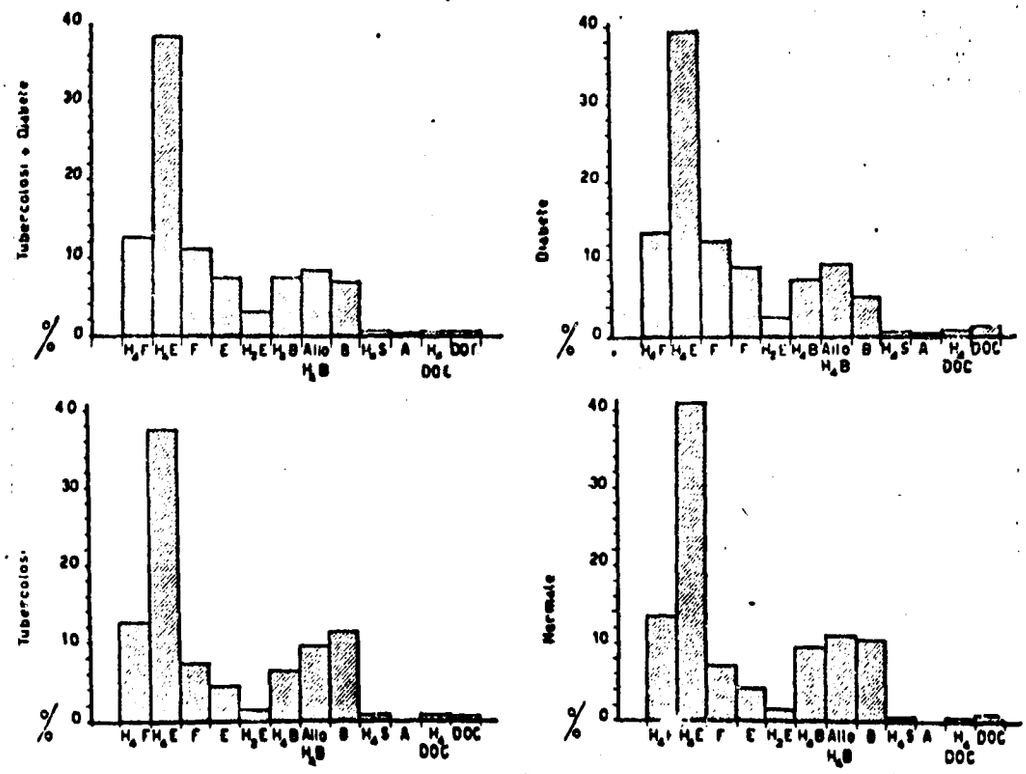


Table 7. - Precentage ratios of the individual fractions of steroids eliminated in the urine.

	Normale	Tubercolosi	Diabete	Tbc. + diabete
H_4F	13.03	12.57	13.83	12.62
H_4E	41.27	37.03	39.70	38.84
F	8.93	7.42	12.40	11.50
E	4.02	4.42	9.03	7.60
B	10.43	11.21	5.14	7.10
H_4B	8.22	6.48	7.25	7.80
allo H_4B	11.40	9.74	9.30	8.40
DOC	0.58	0.51	0.81	0.52
H_4DOC	0.42	0.62	0.53	0.52
E/H_4E	0.10	0.12	0.23	0.19
F/H_4F	0.64	0.59	0.90	0.90
B/H_4B	1.14	1.73	0.70	0.91
B/allo H_4B	0.91	1.14	0.55	0.84
DOC/H_4DOC	1.51	0.82	1.53	1.00
Gruppo E + gruppo F	63.27	62.34	74.96	70.76
Gruppo B	30.96	27.40	21.69	23.30
Rapp. E + F/B	2.11	2.37	3.45	3.04

should be sought rather in the study of the qualitative aspects of the adrenal cortex function, rather than in its size.

We were able, in fact, to show that the chromatographic profile in our patients was consistently and uniformly altered, quite apart from the total quantity of steroids in the urine. We have shown that, by comparison with the normal individual, the tuberculosis patient has a higher level of glycoactive hormones in the urine, accompanied by an equally consistent and relatively marked diminution of the mineral-active hormones, particularly DOC.

At the same time, while the relationship with the respective H_4 derivatives is heightened for the glycoactive group, for DOC we see a clear lowering (about 50%) in the ratio, not only because of a marked drop in elimination of DOC as such, but also by reason of a simultaneous increase in the proportion of H_4 derivatives of the hormone.

This observation led us to seek a relationship between the higher level of inactive substances eliminated in the urine and the asthenic symptom we mentioned.

In this connection, we believe case 14 is significant. The chromatographic profile is basically similar to that of our case 17, to which we have already referred. From a comparative examination of the two, however, we found a marked difference in the amount of total steroid elimination. While the former was the case marked by the highest excretion levels for corticosteroids, the latter had the lowest. Profound asthenia is the symptom clearly common to both cases, hence it can be given adequate pathogenic interpretation in the qualitative variations in adrenal cortex secretion.

We reached much the same conclusion in our study of subjects affected with associated tuberculosis and diabetes mellitus. As we explained earlier, we chose these patients for study because in our efforts to isolate the functional condition of the adrenal cortex as a pathogenic moment in the onset of tuberculosis, we were struck by the contrast between the kind of adrenal insufficiency we had encountered in tuberculosis patients and the highly abnormal pattern common to diabetics.

Several writers have reported that the onset of tuberculosis occurs frequently in diabetic subjects on the occasion of comatose episodes(57). Still others have reported TB onset in subjects whose diabetic condition required large doses of insulin (56). Obviously, the marked hypercortical condition that com-

monly accompanies this morbose situation can be assumed to be a pathogenic factor. However, to seek to attribute to this temporary hypercorticism a determining value seems to us altogether unjustified. A more acceptable hypothesis would be the view that the inevitable phase of exhaustion which follows such undoniably stressful situations (with the overall adaptation syndrome then occurring) might be the agent directly responsible for the emergence of the disease.

As for the qualititative variations in adrenal secretion in pulmonary tuberculosis, we found the study of tubercular diabetics particularly useful. Scrutiny of the chromatographic profile of the tubercular diabetic lends itself to a consideration we find extremely interesting: by comparison with the non-tubercular diabetic, the profile shows no divergence in the glycoactive fractions. The rise in these fractions, along with the decline in the group B steroids, constitutes the pattern of the diabetic state. Where the profiles do differ, however, is in the DOC fraction, which is always markedly diminished in the tubercular diabetic. For this fraction, this is precisely what we expect in the classic pattern of tuberculosis.

It is therefore evident that the chromatographic profile can show us the characteristics peculiar to these particular morbose situations.

We should like to look forward to the possibility of extending such inquiries into other pathological situations, with a view to providing recognizable, characteristic pattern to clinical situations that may be quite different, yet share a common physiopathological denominator.

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